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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,481	SALES AMILL ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/15/07.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3,5-18,20,22,32,34 and 35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,5-18,20,22,32,34 and 35 is/are rejected.

7)☒ Claim(s) 1, 3, 10, 17, 22 and 34-35 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 18 December 2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 3/5/02, 5/15/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Please note that the Examiner in this application has changed. The new Examiner, Christine Foster, may be reached at 571-272-8786.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/15/07 has been entered. Claims 1, 7, 9, 18, and 20 have been amended. Claim 21 was canceled. Claims 1-3, 5-18, 20, 22, 32, 34 and 35 are currently pending and under examination.

Objections/Rejections Withdrawn

2. The rejections of claims 9 and 18 under 35 USC 112, 2nd paragraph and under 35 USC 112, 1st paragraph (scope of enablement) have been withdrawn in response to Applicant's amendments to recite *fragments of C4BP that bind protein S* and in light of Applicant's arguments (Reply, pages 7-10) that the protein S binding site on C4BP was well known in the art at the time of the invention.

3. The rejections of claims 1-3, 7, and 10-11 under 35 USC 102(b) as being anticipated by Cambiaso et al., and of claims 5-6, 8-9, 12-17, and 32 under 35 USC 103(a) as being unpatentable over Cambiaso et al., have been withdrawn in response to Applicant's amendments

to claim 1 to specify the components of the second complex in part (d), for which support was found in Figures 1c and 2c.

4. The rejections of claims 18, 20-22, and 34-35 under 35 USC 103(a) as being unpatentable over Cambiaso et al. have been withdrawn in response to Applicant's amendments to claim 18 to specify that the second member and the third member do not bind each other.

Information Disclosure Statement

5. Applicant's Information Disclosure Statement filed **5/15/07** has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

6. Applicant also requested that the Examiner consider the IDS submitted on **2/15/02**. It appears that Applicant is referring to the IDS citing a non-patent publication by Deffert et al., which was received by the Office on **3/5/02**. The Examiner has considered the reference as indicated by the attached signed copy.

Claim Objections

7. Claims 1, 3, 10, 17, 22 and 34-35 are objected to because of the following informalities:

8. Claim 1 refers to "the first member in the sample" in part (b). There is insufficient antecedent basis for this limitation since the claim does not previously recite that the first member is present *in the sample*. It is suggested that Applicant clarify that the sample is being analyzed for the presence of the first member. For example, the preamble could be amended to refer to "...a first member of a binding pair in a sample...".

9. Claim 3 refers to "the first and second particle", which should apparently read --the first and second particles-- in the plural.

10. Claim 10 recites "CSF"; it is suggested that this abbreviation spelled out in the first instance in the claims.

11. Claim 17 contains a typographical error of the word "ratio".

12. Claim 22 is objected to because it depends from a canceled claim. For the purposes of examination the claim was assumed to depend from claim 18.

13. Claims 34-35 refer to "the size of the first particle and the second particle", which should apparently read --the sizes-- in the plural.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 3, 8-9, 17-18, 20, 22, 32, and 34-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

16. Claim 3 (see the amendments of 8/4/04) recite that at least one of the particles "**comprises**" latex. As originally filed, the claim recited that the first and/or second particle "**is**" latex". This amendment broadens the scope of the original claim to include not only latex

particles but also particles that include latex as well as additional components. Support for this broadening amendment drawn to particles that "comprise" latex (rather than particles that *are* latex) could not be found in the specification.

17. Similarly, claim 8 and 18 recite that the first member "**comprises**" Protein S (see the amendments filed 4/15/05). Claims 8 and 19 as originally filed recited that the first member "**is**" protein S (the limitations of claim 19 have now been incorporated into claim 18). Applicant's reply of 4/15/05 indicated that support may be found at paragraphs 31, 33, 44-45, 52-53, and 70, and in Figure 1 (Reply, page 6). However, support could not be found where indicated for first members that "comprise" Protein S.

The amendments broaden the scope of the claims, since second members that "comprise" Protein S would include not only Protein S *per se* but also polypeptides having an unlimited number of additional amino acids and/or additional components in addition to the Protein S sequence, e.g. fusion proteins, modified forms, etc. The disclosure of Protein S *per se* fails to convey evidence of possession of the claimed members that *comprise* Protein S but which may include other additional components or amino acid sequences.

18. Claims 9 and 18 recite that the second member "**comprises** C4b-binding protein (C4BP) **or a fragment of C4BP that binds to protein S**" (see the instant amendments and the amendment filed 4/15/05).

Applicant's reply does not specifically indicate where support may be found in the specification for the instant amendments to specify that the fragment of C4BP is "***a fragment that binds protein S***", and support could not be found for this limitation. There is no disclosure of those fragments of C4BP that bind to protein S. Limitation of a class, generically disclosed, to

a subgenus without any teaching of the subgenus is new matter unsupported by the specification. Ex parte Batchelder, 131 USPQ 38, 39 (1960).

Applicant's reply of 4/15/05 indicated that support may be found at paragraphs 31, 33, 44-45, 52-53, and 70, and in Figure 1 (Reply, page 6). However, support could not be found where indicated. Although paragraph 33 mentions that the second member may be a "fragment of a protein or polypeptide", fragments of C4BP are not disclosed. This generic disclosure fails to adequately describe fragments of ***C4BP***, and in particular fails to adequately describe ***fragments of C4BP that bind to protein S*** as now claimed.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05. As noted above, limitation of a class, generically disclosed, to a subgenus without any teaching of the subgenus is new matter unsupported by the specification.

The claims also represent new matter for the following reasons. The specification and claims as originally filed disclose a second member that "**is**" C4BP. In particular, it is noted that claim 9 as originally filed recited that the second member "is" C4BP. Similarly, original claim 19 (the limitations of which are now incorporated into claim 18) recited that the second member "is" C4BP. The amendments of 4/15/05 introduced the limitations that the second binding member "**comprises**" C4BP **or a fragment thereof**. The current use of open transitional language conveys a difference in scope, since second members that "comprise" C4BP would include polypeptides having an unlimited number of additional amino acids and/or additional components in addition to C4BP, e.g. fusion proteins, modified forms, etc. As such, the claims broaden the scope of the original disclosure, and therefore represent new matter. The disclosure

of C4BP *per se* fails to convey evidence of possession of the claimed members that *comprise* C4BP.

19. Claim 17 recites that "the third member and the free first member in the sample are in a molar ration [sic] of between about 10 and 40" (see the amendments of 5/17/04). As originally filed, the claim recited that "the molar ratio of third member is between about 10 and 40 times the amount of free first member in the sample". The amendments represent new matter because the claim is now ambiguous as to what the recited ratio refers to (see rejection under 112, 2nd paragraph below). The claim could be interpreted to mean either that the ratio of third member: first member is 10-40, or alternatively that the ratio of first member: third member is 10-40. These are mutually exclusive scenarios (in the first case, the third member is present in a higher amount, while in the second case, the first member is present in a higher amount). However, only the first case is disclosed in the specification (see [0069]). Because the claim could now be interpreted as referring to the use of 10-40X more first binding agent than third binding agent, which is not described in the specification, the claim as amended represents new matter.

20. Claim 18 also recites that "**the second member and the third member do not bind each other**". Applicant's reply indicates that support for the instant amendments may be found at [0042]. However, not support could be found where indicated for the exclusionary proviso that the second and third members do not bind to each other.

Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See In re Johnson, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part

remaining."). See also Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff 'd mem., 738 F.2d 453 (Fed. Cir. 1984). *The mere absence of a positive recitation is not basis for an exclusion.* In the instant case, the specification fails to disclose that the second and the third members do not bind each other as now claimed. The specification also fails to positively recite that the second and third members do bind each other, and therefore does not provide basis for the exclusion of this scenario in the negative limitation now recited.

Because the limitation does not have basis in the original disclosure, the claim fails to comply with the written description requirement. See MPEP 2173.05(i).

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 1-17, 22, 32, and 34-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

23. Claims 1-3, 5-11, 13-17, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: **that the second and third members bind to different binding sites on the first member.**

Claim 1 recites formation of a "second complex comprising the first particle, the second member, the first member, the third member and the second particle, wherein the third member bound to the second particle binds to the first member". As such, the claimed methods require

that the analyte be sandwiched or bound by both the second member and the third member particles in the "second complex" (see especially claim 1, step (d), and Figures 1c and 2c). However, if the second and third members competed with each other for binding the same binding site on the analyte, no such sandwich or "second complex" could be formed since only the second or third members could bind to a single analyte molecule at any given time. It is therefore essential to the performance of the claimed methods that the second and third members recognize different binding sites on the analyte and do not bind competitively.

24. Claims 16-17 recite the limitation "the free first member in the sample". There is insufficient antecedent basis for this limitation in the claims since claim 1 does not refer to a "free" first member.

25. Claim 17 recites that "the third member and the free first member in the sample are in a molar ration [sic] of between about 10 and 40". The claim is indefinite because the wording of the claim is ambiguous and does not make clear what the ratio is referring to, i.e. the ratio of the third member to the first member or alternatively the ratio of the first member to the third member. In other words, it is unclear which of the members is present in the higher amount.

26. Claim 22 recites the limitation "the single binding site to which the second member binds". There is insufficient antecedent basis for this limitation in the claims since there is no prior mention that the second member (C4BP or a fragment thereof) binds to a single binding site.

27. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a method step that accomplishes the purpose of the method as

recited in the preamble of the method. The claim recites "[a] method for diagnosing thrombophilia", but fails to recite any active method steps in which thrombophilia is actually diagnosed. Alternatively, a correlation step may be recited that clearly states how the results of the method achieve the objective of the method as recited in the preamble.

Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. Claims 1-3, 5-7, and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by David et al. (US 4,486,530).

David et al. teach two-site or sandwich immunometric assay techniques for the determination of a first member ("antigenic substance" or "antigen") in a sample (the abstract and column 4, line 50 to 5, line 10; and column 6, line 54 to column 7, line 7, line 2). In particular, the reference teaches assay formats where a first quantity of particles to which a second member ("first monoclonal antibody") is bound is mixed with a second quantity of particles to which a third member ("second monoclonal antibody") is bound (column 9, line 58 to column 10, line 41). When a sample containing the antigen is introduced, agglutination of the particles occurs to form easily detectable particle clumps, which can be used to determine the presence of the antigen, e.g. by detecting the change in turbidity by nephelometry (column 9, line 68 to column 10, line 41). David et al. make clear that agglutination causes an *increase* in

turbidity (see also column 15, lines 52-63). With respect to the limitation that an "unbound form" of the first member is detected, given the broadest reasonable interpretation of such terminology, the teaching in David et al. in which the antigen in the sample is initially not bound to the detection antibodies reads on the claims since the antigen would be considered to be in a form that is not bound to the detection antibodies, i.e. an unbound form.

With respect to claim 2, David et al. teach two or more different antibodies that are each specific to a single antigenic site on the antigen (column 4, lines 50-68).

With respect to claim 3, David et al. teach latex particles (column 10, lines 42-45).

With respect to claims 5-6, David et al. teach that because the second and third members do not interfere with the binding of each other to the antigen, such that both are necessary for formation of the sandwich, both reverse and simultaneous assays can be conducted (column 6, lines 54-67). Simultaneous assays involve a single incubation step in which both antibodies are added to the sample at the same time (in which case steps (a)-(d) would be performed simultaneously), while reverse assays involve stepwise (i.e., sequential) addition of the antibodies (see column 2, lines 34-55).

With respect to claim 7, David et al. teach determining the amount of antigen present in the sample (column 10, lines 37-41).

With respect to claim 10, the reference teaches serum (column 1, lines 13-15).

With respect to claims 11-12, the reference teaches *monoclonal* (as compared to *polyclonal*) antibodies as second and third members; monoclonals bind to a single, specific antigenic site (see also column 6, lines 3-19). The two different monoclonals bind to different binding sites (see for example column 6, lines 54-60).

Claim Rejections - 35 USC § 103

30. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

31. Claims 8-10, 18, 20, 22, 32, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. in view of Giri et al. (Thromb Haemost. 1998 Apr;79(4):767-72, of record).

David et al. is as discussed above, which teaches methods for determination of a first member substantially as claimed in a sandwich-type latex agglutination assay using two monoclonal antibodies as second and third members.

David et al. differs from the claimed invention in that it fails to specifically teach that the first member detected is protein S, or that the second member comprises C4BP or a protein S-binding fragment thereof.

Giri et al. teach that free (unbound) protein S antigen is active as a cofactor to APC and is present at low levels in individuals with protein S deficiency (see in particular the abstract and page 767, the paragraph bridging the left and right columns). The reference further teaches that measurement of free protein S (as compared to total protein S) in plasma has superior predictive value for protein S deficiency, which is related to thrombophilia (page 767, right column, first full paragraph). As such, assays for free protein S are useful for routine clinical purposes to detect protein S deficiencies (the abstract).

The reference also teaches that C4BP (the natural ligand of protein S) and a monoclonal anti-protein S antibody HPS 54 can be used as binding agents to assay specifically for free protein S in a sandwich or two-site assay (see especially page 767, right column, the second full paragraph; page 768, left column; and page 771, "Discussion"; and page 772, the last paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to detect free protein S as the antigen in the method of David et al. One would be motivated to do this because Giri et al. teach that free protein S is associated with disease, and that detection of this antigen can be used for routine clinical purposes to detect protein S deficiencies, which are related to thrombophilia.

With respect to claim 9 and 18, in light of the teachings of Giri et al. that free protein S can be successfully detected using the natural ligand C4BP, it would have been further obvious to substitute C4BP as the second member in place of the monoclonal antibody taught by David et al., for the same purpose of detecting free protein S. To select a known material for their known purpose and obtain the expected results would have been obvious. In addition, one would also be motivated to employ C4BP as the second member in the method of David et al. and Giri et al. because Giri et al. teach that the interaction between protein S and C4BP is very stable (page 771, left column, the fourth paragraph). Furthermore, using CRBP results in an assay that is not influenced by C4BP-protein S complexes (bound form of protein S) or other factors present in plasma (page 771, left column, the last full paragraph).

With respect to the product claims, it would have been further obvious to provide the necessary reagents for performing the method of David et al. and Giri et al. together in composition or kit form for the well-known advantages of convenience and/or commercial sale.

One would have a reasonable expectation of success because the teachings of Giri et al. establish that it is possible to determine free protein S in a sandwich-type assay format using C4BP and a monoclonal antibody. Furthermore, one would have had a reasonable expectation of success in employing the particle-based assay format of David et al. to detect the free protein S antigen taught by Giri et al. because David et al. indicates that the method can be used to detect a wide variety of antigens (column 5, line 55 to column 6, line 2).

With respect to the limitation in claim 18 that the second and third members bind to different sites, Giri et al. teach that C4BP and the anti-protein S monoclonal antibody bind to different sites on protein S since they do not interfere with each other (page 767, right column, the second full paragraph). David et al. also teach that the two antigen-specific reagents should bind to different sites (see for example column 4, lines 50-68). The C4BP and the anti-protein S monoclonal antibody taught by Giri et al. do not bind to each other since the antibody is specific for protein S and not for C4BP.

With respect to claim 22, the anti-protein S monoclonal antibody of Giri et al. (as well as the anti-antigen monoclonal antibodies taught by David et al.) bind to a single site since they are monoclonal.

With respect to claim 32, Giri et al. teach comparing the amount of C4BP-free protein S-antibody complex formed with the amount in healthy controls (see especially Table 3). As discussed above, the reference also teaches that determination of free protein S can be used to detect protein S deficiencies, which are associated with thrombophilia (see especially page 767, right column). Given the known association with disease, it would have been obvious to compare free protein S levels (as indicated by detection of the amount of second complex) with those of

healthy controls as was done by Giri et al. One would be motivated to do this in order to distinguish disease and control subjects. Furthermore, given that protein S deficiencies are associated with thrombophilia, it would have been further obvious to diagnose thrombophilia (or tendency to develop thrombosis) in those subjects found to have protein S deficiencies as measured by low levels of free protein S, given the teachings of Giri et al. that protein S deficiencies are associated with venous thrombosis.

With respect to claim 34, David et al. teach that the latex particles vary in size between about 0.2 to about 10 microns, which overlaps the instantly claimed range (column 10, lines 42-50). In such a case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. MPEP 2144.05.

32. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. in view of Ballas et al. (US 4,812,395).

David et al. is as discussed above, which teaches methods for determination of a first member substantially as claimed in a sandwich-type latex agglutination assay using two monoclonal antibodies as second and third members.

David et al. differs from the claimed invention in that it fails to specifically teach that step (b) is performed within 0 to about 180 seconds.

However, such time periods were disclosed in the prior art in the context of performing agglutination assays. For example, Ballas et al. teach a particle agglutination method in which a particulate reagent is added to the sample and signal is detected 29-46 seconds afterwards (column 19, lines 27-46).

Therefore, it would have been obvious to one of ordinary skill in the art to perform the claimed step within the recited time periods in the course of routine optimization, out of the normal desire of artisans to improve upon what is already known. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (see MPEP 2144.05).

33. Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. in view of Mischak et al. (US 6,124,430).

David et al. is as discussed above, which teaches methods for determination of a first member substantially as claimed in a sandwich-type latex agglutination assay using two monoclonal antibodies as second and third members.

David et al. differs from the claimed invention in that it fails to specifically teach the specific molar ratios of the reagents used, and fails to specifically teach that the third member is present in higher amount than the free member in the sample. The reference also fails to specifically teach the specific molar ratios of the reagents to be used in the assay.

Mischak et al. teaches that in a sandwich-type assay, antibody is typically used in amounts substantially higher than the amount of analyte expected in the sample (see especially column 8, lines 7-10).

Therefore, it would have been obvious to employ an excess of antibody (third member) in the method of David et al. as taught by Mischak et al. One would be motivated to do this in order

to successfully detect analyte, in light of the teachings of Mischak et al. that an excess of antibody is normal practice when performing sandwich-type assays, such as that of David et al.

It would have been further obvious to select concentrations of the reagents for the assay within the claimed molar ratios in the course of routine optimization, out of the normal desire of artisans to improve upon what is already known. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (see MPEP 2144.05).

34. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over David et al. in view of Giri et al. as applied to claim 18 above, and further in view of Cambiaso et al. (US 4,184,849, of record).

David et al. and Giri et al. are as discussed above, which teach a composition or kit for detecting free protein S in a dual particle sandwich-type latex agglutination assay. However, the references fail to specifically teach that the sizes of the first and second particles are different.

Cambiaso et al. teach agglutination assays using two particles (see especially the abstract). The reference teaches that the extent of agglutination can be detected using selective counting techniques, in which case it is highly advantageous that the two particles be of a different size so that they may be distinguished by the counter (column 3, line 44 to column 4, line 37). Such particle counting techniques avoid the need for separation steps, which are time-consuming and may introduce error (column 3, lines 55-65).

Therefore, it would have been obvious to one of ordinary skill in the art to employ first and second particles of different size, as taught by Cambiaso et al., in the composition or kit of David et al. and Giri et al. One would be motivated to do this in order to detect agglutination in the method of David et al. and Giri et al. using a particle counter, which obviates the need for a separation step.

Double Patenting

35. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

36. Claims 1-3 and 5-17 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,379,975 in view of David et al.

The '975 patent claims a method for determining the level of a first member (free protein S) by contacting a second member ("ligand") (which may be C4BP, and which may be linked to

a carrier) with the sample (see especially claims 1-2 and 6-7). Detection may be via a third member (antibody specific for protein S) (see claim 5).

The patent claims differ from the instantly claimed invention in that they do not recite detection by an increase in the turbidity of the sample as a result of particle agglutination. Although in the '975 patent the C4BP may be linked to a carrier, the carrier is not specifically recited to be a particle. Furthermore, the third member (antibody) is not bound to a particle.

However, sandwich-type assay formats involving two particles were known in the art. David et al. (discussed further above) teach two-site or sandwich immunometric assay techniques for the determination of a first member ("antigenic substance" or "antigen") in a sample (the abstract and column 4, line 50 to 5, line 10; and column 6, line 54 to column 7, line 7, line 2). In particular, the reference teaches assay formats where a first quantity of particles to which a second member ("first monoclonal antibody") is bound is mixed with a second quantity of particles to which a third member ("second monoclonal antibody") is bound (column 9, line 58 to column 10, line 41). When a sample containing the antigen is introduced, agglutination of the particles occurs to form easily detectable particle clumps, which can be used to determine the presence of the antigen, e.g. by detecting the change in turbidity by nephelometry (column 9, line 68 to column 10, line 41). David et al. make clear that agglutination causes an *increase* in turbidity (see also column 15, lines 52-63).

Therefore, it would have been obvious to one of ordinary skill in the art to perform the method of the '975 patent by immobilizing both C4BP and antibody on particles, in order to detect free protein S by the sandwich-type agglutination assay format of David et al. One would

be motivated to do this in order to detect the amount of free protein S by nephelometric techniques.

37. Claims 1-3, 5-18, 20, 22, and 34-35 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 7,041,458 in view of David et al.

The '458 patent claims kits for assaying free protein S employing second and third members (C4BP and an antibody for protein S) in a sandwich-type assay format (see especially claims 1 and 24). The second member may be immobilized on a carrier (claims 2-4).

However, the patent claims differ from the instantly claimed invention in that they fail to specifically teach that the second and third members are bound to particles, or that detection is via detection of a change in turbidity of the sample as in instant claim 1.

However, sandwich-type assay formats involving two particles were known in the art. David et al. (discussed further above) teach two-site or sandwich immunometric assay techniques for the determination of a first member ("antigenic substance" or "antigen") in a sample (the abstract and column 4, line 50 to 5, line 10; and column 6, line 54 to column 7, line 7, line 2). In particular, the reference teaches assay formats where a first quantity of particles to which a second member ("first monoclonal antibody") is bound is mixed with a second quantity of particles to which a third member ("second monoclonal antibody") is bound (column 9, line 58 to column 10, line 41). When a sample containing the antigen is introduced, agglutination of the particles occurs to form easily detectable particle clumps, which can be used to determine the presence of the antigen, e.g. by detecting the change in turbidity by nephelometry (column 9, line

68 to column 10, line 41). David et al. make clear that agglutination causes an *increase* in turbidity (see also column 15, lines 52-63).

Therefore, it would have been obvious to one of ordinary skill in the art to immobilize both C4BP and antibody on particles in the kits of the '458 patent, in order to detect free protein S by the sandwich-type agglutination assay format of David et al. One would be motivated to do this in order to detect the amount of free protein S by nephelometric techniques.

38. Claim 32 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,379,975 in view of David et al. as applied to claim 8 above, or alternatively over claims 1-41 of U.S. Patent No. 7,041,458 as applied to claim 8 above, and further in view of Giri et al.

The teachings of the '975 and '458 patents are as discussed above, which fail to specifically teach diagnostic methods.

Giri et al. teach that free (unbound) protein S antigen is active as a cofactor to APC and is present at low levels in individuals with protein S deficiency (see in particular the abstract and page 767, the paragraph bridging the left and right columns). The reference further teaches that measurement of free protein S (as compared to total protein S) in plasma has superior predictive value for protein S deficiency, which is related to thrombophilia (page 767, right column, first full paragraph). As such, assays for free protein S are useful for routine clinical purposes to detect protein S deficiencies (the abstract).

Therefore, given the known association of protein S with disease, it would have been obvious to compare free protein S levels (as indicated by detection of the amount of second

complex) with those of healthy controls as was done by Giri et al. One would be motivated to do this in order to distinguish disease and control subjects. Furthermore, given that protein S deficiencies are associated with thrombophilia, it would have been further obvious to diagnose thrombophilia (or tendency to develop thrombosis) in those subjects found to have protein S deficiencies as measured by low levels of free protein S, given the teachings of Giri et al. that protein S deficiencies are associated with venous thrombosis.

Response to Arguments

39. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection set forth above.

Conclusion

40. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

41. Eda et al. (US 6,248,597 B1) also teaches agglutination assays involving formation of a sandwich complex, where two binding partners can be separately coated on different particles (see especially column 7, lines 20-39).

42. Cragle et al. (US 4,590,169).

43. Varadi et al. (US 5,643,739) is also relevant to claim 32 for its teaching that congenital protein S deficiency causes thrombophilia (column 1, lines 55-65).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The

examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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